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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,494	11/01/2001	Susan E. Conroy	CJ-01353K	7330

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EXAMINER	
VOGEL, NANCY S	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,494	CONROY ET AL.	
	Examiner	Art Unit	
	Nancy Vogel	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-36 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-36 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 01 November 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/19/02.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-36 are pending in the case.

Receipt of the Information Disclosure Statement on 8/19/02 is acknowledged.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: it is not signed by one of the inventors (Susan Conroy).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-26, 29-36 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of

copending Application No. 10/245986 (Conroy) in view of Hansen et al. (US Patent 5,877,302)

This is a provisional obviousness-type double patenting rejection.

Application No. 10/245,986 claims a method to deliver a vector to a cell which is an andenovirus, adeno-associated virus, herpesvirus, lentivirus, or baculovirus, in a combined preparation with dextrin, having a molecular weight of 2000-55,000, at least 10% w/v, degree of polymerization equal to or greater than 1, and compositions comprising said virus and dextrin. The difference between the reference claims and the instant claims is that the instant claims recite the composition comprises a divalent cation such as $MgCl_2$ and a sugar such as sucrose.

However, Hansen et al. disclose that compositions comprising nucleic acids for delivery to cells may contain such compounds as $MgCl_2$ and a sugar such as sucrose, in order to increase stability and efficiency of transfer (see (see column 22, lines 48-53). It would have been obvious to one of ordinary skill in the art to have modified the method and compositions disclosed by Conroy to include sucrose and $MgCl_2$, , because Conroy teach that it is within the ordinary skill in the art to introduce nucleic acids to a cell using a dextrin solution to produce beneficial modifications to the cell, and Hansen, teach that it is within the skill in the art to utilize compounds such as $MgCl_2$, sucrose, in order to facilitate transfer of nucleic acids known to be beneficial to cells, into a cell in need of treatment. One would have been motivated to make these modifications by the benefits of increased stability and transfer of nucleic acids, as disclosed by Hansen. Based upon the teachings of the cited reference, the high skill of one of ordinary skill in

the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Conroy et al. (Proc. American Assoc. for Cancer Res., 41: 524 (March 2000)) or Engler et al. (Clinical Cancer Research, Vol. 6, No. 11, p. 516 (11/1/00) in view of Hansen et al. (US Patent 5,877,302), Verma et al. (Nature, 389 :239-242 (1997)) and Nielsen et al. (US 2003/0064949).

Conroy et al. or Engler et al. each disclose a method of delivering a nucleic acid which is a viral vector wherein the nucleic acid is carried in a solution comprising dextrin (icodextrin) in the molecular weight range 13,000 and 19,000 daltons. The dextrin is present at 4% w/v. The mOsm/L is 282-286. The references disclose compositions comprising said nucleic acid solution and pharmaceuticals comprising said composition.

The reference does not disclose that sucrose and $MgCl_2$ is present, and does not disclose that the vector may adenovirus, retrovirus, herpesvirus, lentivirus, vaccinia virus or baculovirus, and that a tumor suppressor gene such as p53 may be in the viral vector.

However, Hansen et al. disclose that $MgCl_2$ and sucrose may be added to nucleic acids to aid in delivery to cells by decreasing the size of the DNA complex and to increase its stability (see column 22, lines 48-53). Verma et al. disclose viral vectors such as lentivirus, retrovirus, adenovirus, adeno-associate virus, herpes simplex virus, vaccinia virus for the delivery of nucleic acids to cells (see entire article). Nielson et al. disclose the delivery of the tumor suppressor p53 in an adenoviral vector (see page 1 paragraph 9 and 10, page 2, paragraph 14), and disclose that suitable pharmaceutically acceptable carriers which may contain carbohydrates such as glucose, sucrose, dextrans, may be use (see page 9 paragraph 117).

It would have been obvious to one of ordinary skill in the art to have modified the method and compositions disclosed by Conroy or Engler, to include sucrose and $MgCl_2$, and to utilize any known viral vector, and to include a tumor suppressor such as p53, as disclosed by Hansen, Verma and Nielson, because Conroy and Engler teach that it is

within the ordinary skill in the art to introduce nucleic acids to a cell using a dextrin solution to produce beneficial modifications to the cell, and Hansen, Verma and Nielson teach that it is within the skill in the art to utilize compounds such as $MgCl_2$, sucrose, viral vectors, and the p53 gene, in order to facilitate transfer of nucleic acids known to be beneficial to cells, into a cell in need of treatment. One would have been motivated to make these modifications by the benefits of increased stability and transfer of nucleic acids, the known benefits of viral vectors whose structure is well known and which efficiently transfer DNA to cells, and the known benefits of supplying the tumor suppressor p53 to cancer cells, as disclosed by Hansen, Verma and Nielson. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davies et al. (GB 2 207 050 A) in view of Hansen et al. (US Patent 5,877,302), Verma et al. (Nature, 389 :239-242 (1997)) and Nielsen et al. (US 2003/0064949).

Davies et al. disclose a method to deliver drugs to a cell wherein the drug is carried in a solution comprising dextrin (glucose polymer), wherein the degree of dextrin polymerization of greater than 12, the molecular weight average is between 15,00 and 25,000 and the concentration of the glucose polymer may be 0.5 – 10% w/v (see abstract and pages 8-9). The solution may contain Mg (see page 6). The reference discloses that the invention has application for any drug (page 10). The reference

discloses compositions comprising said nucleic acid solution and pharmaceuticals comprising said composition

The reference does not disclose that sucrose is present, does not disclose that the "drug" may be nucleic acid, and does not disclose that a viral vector may be used which is adenovirus, retrovirus, herpesvirus, lentivirus, vaccinia virus or baculovirus, and that a tumor suppressor gene such as p53 may be in the viral vector.

However, Hansen et al. disclose that $MgCl_2$ and sucrose may be added to nucleic acids to aid in delivery to cells by decreasing the size of the DNA complex and to increase its stability (see column 22, lines 48-53). Verma et al. disclose the delivery of beneficial nucleic acids to cells via viral vectors such as lentivirus, retrovirus, adenovirus, adeno-associate virus, herpes simplex virus, vaccinia virus for the delivery of nucleic acids to cells (see entire article). Nielson et al. disclose the delivery of the tumor suppressor p53 in an adenoviral vector (see page 1 paragraph 9 and 10, page 2, paragraph 14), and disclose that suitable pharmaceutically acceptable carriers which may contain carbohydrates such as glucose, sucrose, dextrans, may be use (see page 9 paragraph 117).

It would have been obvious to one of ordinary skill in the art to have modified the method and compositions disclosed by Davies et al., to include nucleic acids such as viral vectors comprising a gene known to be beneficial to a cell in need of treatment, said nucleic acid falling into the definition of "drug", as taught by Verma et al. It would have been further obvious to include sucrose and $MgCl_2$, and to utilize any known viral vector, and to include a tumor suppressor such as p53, as disclosed by Hansen, Verma

and Nielson, because Davies et al. teach that it is within the ordinary skill in the art to introduce a drug to a cell using a dextrin solution to produce beneficial modifications to the cell, and Hansen, Verma and Nielson teach that it is within the skill in the art to utilize compounds such viral vectors comprising beneficial genes such as p53, and further to include $MgCl_2$, sucrose, in order to facilitate the transfer of nucleic acids known to be beneficial to cells, into a cell in need of treatment. One would have been motivated to make these modifications by the benefits of increased stability and transfer of nucleic acids, the known benefits of viral vectors whose structure is well known and which efficiently transfer DNA to cells, and the known benefits of supplying the tumor suppressor p53 to cancer cells, as disclosed by Hansen, Verma and Nielson. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Conroy et al. (US 2003/0039960 A1) in view of Hansen et al. (US Patent 5,877,302), Verma et al. (Nature, 389 :239-242 (1997)) and Nielsen et al. (US 2003/0064949).

Conroy et al. disclose a method of delivering a nucleic acid which is a viral vector which is adeno-associated virus wherein the nucleic acid is carried in a solution comprising dextrin (icodextrin) in the molecular weight range 13,000 and 19,000 daltons. The dextrin is present at 4% w/v. The mOsm/L is 282-286. (see page 2,

paragraph 18 – page 3, paragraph 42). The reference discloses compositions comprising said nucleic acid solution and pharmaceuticals comprising said composition.

The reference does not disclose that sucrose and $MgCl_2$ is present, and does not disclose that the vector may adenovirus, retrovirus, herpesvirus, lentivirus, vaccinia virus or baculovirus, and that a tumor suppressor gene such as p53 may be in the viral vector.

However, Hansen et al. disclose that $MgCl_2$ and sucrose may be added to nucleic acids to aid in delivery to cells by decreasing the size of the DNA complex and to increase its stability (see column 22, lines 48-53). Verma et al. disclose viral vectors such as lentivirus, retrovirus, adenovirus, adeno-associate virus, herpes simplex virus, vaccinia virus for the delivery of nucleic acids to cells (see entire article). Nielson et al. disclose the delivery of the tumor suppressor p53 in an adenoviral vector (see page 1 paragraph 9 and 10, page 2, paragraph 14), and disclose that suitable pharmaceutically acceptable carriers which may contain carbohydrates such as glucose, sucrose, dextrans, may be used (see page 9 paragraph 117).

It would have been obvious to one of ordinary skill in the art to have modified the method and compositions disclosed by Conroy to include sucrose and $MgCl_2$, and to utilize any known viral vector, and to include a tumor suppressor such as p53, as disclosed by Hansen, Verma and Nielson, because Conroy teach that it is within the ordinary skill in the art to introduce nucleic acids to a cell using a dextrin solution to produce beneficial modifications to the cell, and Hansen, Verma and Nielson teach that it is within the skill in the art to utilize compounds such as $MgCl_2$, sucrose, viral vectors,

and the p53 gene, in order to facilitate transfer of nucleic acids known to be beneficial to cells, into a cell in need of treatment. One would have been motivated to make these modifications by the benefits of increased stability and transfer of nucleic acids, the known benefits of viral vectors whose structure is well known and which efficiently transfer DNA to cells, and the known benefits of supplying the tumor suppressor p53 to cancer cells, as disclosed by Hansen, Verma and Nielson. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to deliver nucleic acid to a cell intraperitoneally using a particular dextrin solution, does not reasonably provide enablement for methods of delivery of nucleic acids to a cell under any other conditions than intraperitoneally, using the recited dextrin solution. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The present claims are very broad. The claims recited a method of delivery of nucleic acids to any cell using a dextrin/sugar solution, without specifying the actual method of delivery.

The nature of the invention is a method of delivery of nucleic acid in vivo. The delivery of a nucleic acid in vivo or ex vivo for therapeutic reasons constitutes gene therapy.

An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, Verma et al (Nature (1997) 389:239-242) and Palu et al. (J. Biotechnol. (1999) 68:1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al. p. 239, 1st paragraph; Palu et al. p. 1, Abstract. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. While both references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. See Verma et al. p. 242, col. 2-3. While applicants have shown intraperitoneal administration of nucleic acids in a particular dextrin/sucrose solution using a particular results in some transfer of said nucleic acids to cells, the specification does not provide support for administration of the recited nucleic acid/dextrin/sucrose solution to cells via any other method. As stated in Verma, the delivery of nucleic acids to cells suffers from poor efficiency and transient expression of the gene (p. 239, col. 3, 2nd paragraph).

Likewise, Luo et al. (Nature Biotechnology 18 : 33-37, 2000) indicates that non-viral synthetic delivery systems are very inefficient. See p. 33, Abstract and col. 1, 1st and 2nd paragraph. Thus, such techniques are not routine and predictable.

The relative skill of those in the art of stem cell culture and recombinant DNA technology is high.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. Indeed, the recent tragic and unexpected death of a participant in a gene therapy clinical trial clearly illustrates the unpredictable nature of gene therapy. See Fox, ASM News, Feb. 2000, 66 (2):1-3. The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

The present specification provides little or no guidance to support the scope of the claimed invention for gene therapy applications. The specification discloses several examples utilizing intraperitoneal administration of a nucleic acid in the disclosed dextrin/sucrose/Mg solution, and its effect on two types of tumors in mice. However, there is no guidance provided for any other type of administration. There is no direction provided as to how to overcome the obstacles to gene therapy recognized by leaders in the field, i.e. transient gene expression.

The working examples disclosed directed toward in vivo treatment are the intraperitoneal administration of nucleic acids comprising the p53 gene to treat prostate and ovarian tumor in mice.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method of gene therapy to treat a condition, one of skill in the art would have to determine how to administer the disclosed composition comprising nucleic acids and a dextrin/sucrose/Mg solution, appropriate vectors, appropriate concentrations of vectors, appropriate timing of administration, etc. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of the experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to make and/or use the claimed methods of administration of nucleic acids to cells using any method other than the disclosed intraperitoneal administration of the disclosed vectors, using the dextrin/sucrose/Mg solution utilized in the examples.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-30 are drawn to methods, but no positive method steps are recited. Therefore the metes and bounds of the intended subject matter cannot be determined. The claims have been examined as if they contain the positive method steps recited in claim 36.

Claims 24 and 32 are vague and indefinite in the recitation of "derived from", since the number and types of steps in the deriving are not known.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 6:30 - 3:00, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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3/2/04

JAMES KETTER
PRIMARY EXAMINER